Multi-component reaction between cyclohexyl isocyanide, cyanoacetic acid and aldehyde: synthesis of methyl 2-cyano-3-(aryl)-cyclohexylcarbamoyl-(aryl)-acrylate

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An improved multi-component reaction of cyclohexyl isocyanide is described. The reaction between two equivalents of an aldehydes, cyclohexyl isocyanide and cyanoacetic acid at room temperature leads to methyl 2-cyano-3-(aryl)-cyclohexylcarbamoyl-(aryl)-acrylate in good yields.

Keywords: cyclohexyl isocyanide, multi-component reaction, aldehydes, cyanoacetic acid

Modern synthetic design demands high efficiency in terms of minimisation of synthetic steps together with maximisation of complexity.[1] One way to fulfill these goals is the use of multicomponent reactions (MCRs) that consist of several simultaneous bond-forming reactions which allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner.[2–4] New strategies for the synthesis of complex molecular structures from easily available substrates by short and effective routes have been investigated. The most important of these strategies has been the developing of MCRs, a reaction in which three or more compounds connect together by covalent bonds to produce a complex molecule containing the main structure of all the starting materials. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses. Coupled with high-throughput library screening, this strategy has been important for the rapid identification and optimisation of biologically active lead compounds.[5–13] Among the MCRs, isocyanide based multi-component reactions (IMCRs) have gained the most attention by organic chemists. Ugi four component reaction(U-4CR)[10–12] and Passerini three component reaction (P-3CR)[14] are among the most important IMCRs. U-4CR and P-3CR describe the reaction of isocyanides with carboxylic acids in the presence of imines or aldehydes, respectively.

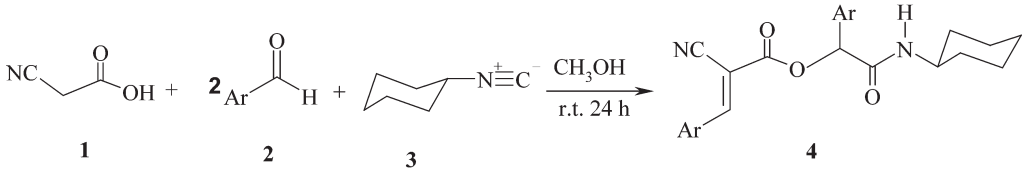
A wide variety of electrophiles have been used to trap isocyanide-DMAD intermediates, among them are carbon electrophiles such as aldehydes, imines, quinonoids,[15] 1,2-diketones,[16] 1,2,3-tricarbonyl compounds,[17] isocyanates,[18] and hydrogen electrophiles such as pyrrole,[19] amides,[20] hydroxy coumarine,[21] phenoles,[22] phthalic anhydride,[23] and isatoic anhydride.[24] Treatment of isocyanide-DMAD zwitterion with aromatic carboxylic acids has been reported to produce unsaturated amides.[25] Reaction of isocyanide-DMAD adduct with aromatic-substituted acetic acids has been reported to afford 2,5-diaminofuran derivatives in the presence of two equivalents of an isocyanide.[26] In the context of our previous works on IMCRs[19–21,27], we report here the results of our investigations on the reaction of cyclohexyl isocyanide, cyanoacetic acid and aromatic aldehydes.

Results and discussion

Treatment of aldehyde (2 equiv.) with cyanoacetic acid (1 equiv.) and cyclohexyl isocyanide (1equiv.) in methanol for 24 h at room temperature, after silica gel column chromatography afforded methyl 2-cyano-3-(aryl)-cyclohexylcarbamoyl-(aryl)-acrylate (**4**) in excellent yields (Scheme1).

The structures of compounds **4a-d** were deduced from their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values.

The ^{1}H NMR spectrum of compound **4a** was simple and exhibited two sharp single lines, which are respectively due to olefinic and methine protons (δ = 8.63 and 6.16 ppm) and one NH group (δ = 7.81 ppm, disappeared with addition of D_2O). Cyclohexyl fragment protons resonated as multiplets at δ = 1.06–1.74 and a multiplet at δ = 3.47 ppm and aromatic protons resonated at δ = 7.42–8.81 ppm. The ^{13}C NMR spectrum of compound **4a** showed 20 distinct resonances in agreement with the proposed structure. The IR spectrum showed an absorption bond at 3230 cm^{-1} for the NH group. The carbonyl stretching vibrations were observed as strong absorption bonds at 1743 and 1658 cm^{-1}. The nitrile stretching vibrations were



4	Ar	yield%*
a	p-NO_2-phenyl	92
b	m-CH_3O-phenyl	89
c	o-CH_3O-phenyl	90
d	p-Cl-phenyl	89

* Isolated yields

Scheme 1 Reaction between aldehydes, cyanoacetic acid and cyclohexyl isocyanide.

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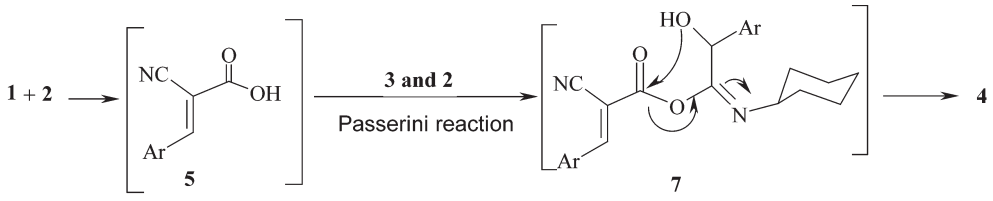

Scheme 2 Suggested mechanism for formation of compound **4**.

observed as an absorption bond at 2241 cm^{-1}. The molecular ion peak at 478 in the mass spectrum of compound **4a** supported the 2:1:1 adduct of aldehydes, cyanoacetic acid and cyclohexyl isocyanide.

On the basis of the well established chemistry of isocyanides[6–8,22] it is reasonable to assume that intermediate **5** is produced by initial Knoevenagel condensation of aldehyde with cyanoacetic acid which is then converted to product **4** during a Passerini reaction with isocyanide and another molecule of aldehyde (Scheme 2).

In conclusion, we report here the multicomponent reaction between aldehydes, cyanoacetic acid and cyclohexyl isocyanide as a simple and efficient route for the synthesis of methyl 2-cyano-3-(aryl)-cyclohexylcarbamoyl-(aryl)-acrylate. The advantages of this method are that it is inexpensive, has easily available starting materials, simple and neutral reaction conditions, high yields, single-product reaction and simple work-up processes.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser at the analytical laboratory of Islamic Azad University Yazd branch. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure:
To a magnetically stirred solution of aldehyde (2mmol) and cyanoacetic acid (1 mmol) in 15 ml methanol was added a mixture of cyclohexyl isocyanide (1 mmol) in 1 mL methanol at room temperature. The reaction mixture was then stirred for 24 h. The solvent was removed and the residue was purified by silica gel column chromatography using hexane–ethyl acetate as eluent. The solvent was removed under reduced pressure to afford the product.

Methyl 2-cyano-3-(4-nitrophenyl)-cyclohexylcarbamoyl-(4-nitrophenyl)-acrylate: **(4a):** Yield (92%); white powder, m.p. 229–231 °C, IR (KBr) (ν_{max}, cm^{-1}): 3230 (NH), 2241 (C=N), 1743, 1658 (C=O). Anal.Calcd for $C_{24}H_{22}N_4O_7$: C, 60.25; H,4.63; N,11.71. Found: C, 60.38; H, 4.52; N,11.63%. MS (*m/z*,%): 478 (M^+,12). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.06–1.74 (10 H, m, 5 CH_2 of cyclohexyl), 3.47 (1 H, m, CH of cyclohexyl), 6.16 (1 H, s, CH), 7.81 (1 H, d, $^3J_{HH}$ = 7.5 Hz, NH), 7.42–8.81 (8H, m, aromatic), 8.63 (1 H, s, C=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ 25.11, 25.20, 25.94, 32.76, 33.05 and 48.80 (5 CH_2 and CH of cyclohexyl), 76.80 (CH),115.58 (CN), 106.87 and 137.97 (C=CH) 124.59,125.09, 129.06, 132.72, 142.99, 148.56, 150.29, 154.47 (8C aromatic), 161.18 and 166.05 (2*C*O) ppm.

Methyl 2-cyano-3-(3-methoxyphenyl)-cyclohexylcarbamoyl-(3-methoxyphenyl)-acrylate: **(4b):** Yield (89%); white powder, m.p. 189–191 °C, IR (KBr) (ν_{max}, cm^{-1}): 3270 (NH), 2238 (C=N), 1736, 1655 (C=O). Anal.Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.80; H, 6.14; N, 6.31%. MS (*m/z*,%): 448 (M^+, 7). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.25–1.94 (10 H, m, 5 CH_2 of cyclohexyl), 3.79 (1 H, m, CH of cyclohexyl), 3.82, 3.87 (6H, 2s, 2OCH_3), 6.14 (1 H, s, CH), 6.39 (1 H, d, $^3J_{HH}$ = 7.5 Hz, NH), 6.89–7.60 (8H, m, aromatic), 8.23 (1 H, s, C=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ 24.97, 25.02, 25.83, 33.14, 33.21 and 48.63 (5 CH_2 and CH of cyclohexyl), 55.74 and 55.91 (2OCH_3), 79.05 (CH),116.13 (CN), 102.26 and 136.93 (C=CH), 113.34, 115.01, 115.39, 119.92, 121.24, 124.99, 130.36, 130.81, 132.77, 156.94, 160.27 and 160.89 (12C aromatic), 160.49 and 166.72 (2*C*O) ppm.

Methyl 2-cyano-3-(2-methoxyphenyl)-cyclohexylcarbamoyl-(2-methoxyphenyl)-acrylate: **(4c):** Yield (90%); white powder, m.p. 207–209 °C, IR (KBr) (ν_{max}, cm^{-1}): 3405 (NH), 2245 (C=N), 1747, 1673 (C=O). Anal.Calcd for $C_{26}H_{28}N_2O_5$: C, 69.63; H, 6.29; N, 6.25. Found: C, 69.80; H, 6.14; N, 6.31%. MS (*m/z*,%): 448 (M^+, 6). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.18–1.93 (10 H, m, 5 CH_2 of cyclohexyl), 3.87 (1 H, m, CH of cyclohexyl), 3.33, 3.84 (6H, 2s, 2OCH_3), 4.97 (1 H, s, CH), 6.71 (1 H, d, $^3J_{HH}$ = 7.5 Hz, NH), 6.89–7.58 (8H, m, aromatic), 8.21 (1 H, s, C=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ 25.24, 25.27, 26.01, 33.48, 33.65 and 47.99 (5 CH_2 and CH of cyclohexyl), 56.14 and 57.61 (2OCH_3) 111.68, 115.03, 116.67, 119.94, 121.20, 126.32, 129.27, 130.19, 131.31, 156.73, 156.88 and 158.39 (12C aromatic), 79.08 (CH), 115.87 (CN), 102.26 and 135.05 (C=CH), 160.53 and 170.19 (2*C*O) ppm.

Methyl 2-cyano-3-(4-chlorophenyl)-cyclohexylcarbamoyl-(4-chlorophenyl)- acrylate: **(4d):** Yield (89%); White powder, m.p. 201–203 °C, IR (KBr) (ν_{max}, cm^{-1}): 3285 (NH), 2225 (C=N), 1728, 1658 (C=O). Anal.Calcd for $C_{24}H_{22}Cl_2N_2O_3$: C, 63.03; H, 4.85; N, 6.13. Found: C, 62.89; H, 4.99; N, 6.01%. MS (*m/z*,%): 456 (M^+, 11). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.06–1.72 (10 H, m, 5 CH_2 of cyclohexyl), 3.45 (1 H, m, CH of cyclohexyl), 5.98 (1 H, s, CH), 7.88 (1 H, d, $^3J_{HH}$ = 7.5 Hz, NH), 7.47–8.25 (8H, m, aromatic), 8.44 (1 H, s, C=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ 25.15, 25.24, 25.97, 32.82, 32.07 and 48.65(5 CH_2 and CH of cyclohexyl), 76.83 (CH),116.09 (CN), 103.57 and 135.05 (C=CH) 129.44, 129.80, 130.45, 132.04, 133.47, 134.36, 139.17, 155.28 (8C aromatic), 161.77 and 166.7 5 (2*C*O) ppm.

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